Induced pluripotent stem cell models of Zellweger spectrum disorder show impaired peroxisome assembly and cell type-specific lipid abnormalities.

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Authors: Xiao-Ming Wang, Wing Yan Yik, Peilin Zhang, Wange Lu, Ning Huang, Bo Ram Kim, Darryl Shibata, Madison Zitting, Robert H Chow, Ann B Moser, Steven J Steinberg, Joseph G Hacia

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Public Summary:
We propose that induced pluripotent stem cells could assist investigations into the cell type-specificity of peroxisomal activities, toxicology studies, and in HCS for targeted therapies for peroxisome-related disorders.

Scientific Abstract:
INTRODUCTION: Zellweger spectrum disorder (PBD-ZSD) is a disease continuum caused by mutations in a subset of PEX genes required for normal peroxisome assembly and function. They highlight the importance of peroxisomes in the development and functions of the central nervous system, liver, and other organs. To date, the underlying bases for the cell-type specificity of disease are not fully elucidated. METHODS: Primary skin fibroblasts from seven PBD-ZSD patients with biallelic PEX1, PEX10, PEX12, or PEX26 mutations and three healthy donors were transduced with retroviral vectors expressing Yamanaka reprogramming factors. Candidate induced pluripotent stem cells (iPSCs) were subject to global gene expression, DNA methylation, copy number variation, genotyping, in vitro differentiation and teratoma formation assays. Confirmed iPSCs were differentiated into neural progenitor cells (NPCs), neurons, oligodendrocyte precursor cells (OPCs), and hepatocyte-like cell cultures with peroxisome assembly evaluated by microscopy. Saturated very long chain fatty acid (sVLCFA) and plasmalogen levels were determined in primary fibroblasts and their derivatives. RESULTS: iPSCs were derived from seven PBD-ZSD patient-derived fibroblasts with mild to severe peroxisome assembly defects. Although patient and control skin fibroblasts had similar gene expression profiles, genes related to mitochondrial functions and organelle cross-talk were differentially expressed among corresponding iPSCs. Mitochondrial DNA levels were consistent among patient and control fibroblasts, but varied among all iPSCs. Relative to matching controls, sVLCFA levels were elevated in patient-derived fibroblasts, reduced in patient-derived iPSCs, and not significantly different in patient-derived NPCs. All cell types derived from donors with biallelic null mutations in a PEX gene showed plasmalogen deficiencies. Reporter gene assays compatible with high content screening (HCS) indicated patient-derived OPC and hepatocyte-like cell cultures had impaired peroxisome assembly. CONCLUSIONS: Normal peroxisome activity levels are not required for cellular reprogramming of skin fibroblasts. Patient iPSC gene expression profiles were consistent with hypotheses highlighting the role of altered mitochondrial activities and organelle cross-talk in PBD-ZSD pathogenesis. sVLCFA abnormalities dramatically differed among patient cell types, similar to observations made in iPSC models of X-linked adrenoleukodystrophy. We propose that iPSCs could assist investigations into the cell type-specificity of peroxisomal activities, toxicology studies, and in HCS for targeted therapies for peroxisome-related disorders.